2006 Annual Meeting Report:
Centers for Medical Countermeasures against Radiation (CMCR) Program

Division of Allergy, Immunology and Transplantation (DAIT)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)

CMCR Awardees

To expand the medical options available to triage, prevent and/or treat unintentional, radiation-induced injury, NIH established eight Centers for Medical Countermeasures against Radiation (CMCRs) in September 2005. These Centers include Columbia University, Dana Farber Cancer Institute, Duke University, Fred Hutchinson Cancer Research Center, Medical College of Wisconsin, University of California, Los Angeles, University of Pittsburgh, and the University of Rochester.

Purpose of the Meeting

The primary objective was for the Centers to present research progress made during the first 9 months of the program. Other goals included fostering continued, synergistic interactions among the Centers, and facilitating interactions between the Centers, government and commercial laboratories. The meeting was held June 7-8, 2006 at the Gaithersburg Hilton in Gaithersburg, Maryland, and presentations were divided into 5 sessions: Session I – Identification & Development of Countermeasures (Early & Late Radiation Effects Countermeasures Development , Cell-Based Therapies, and High Throughput Screening), Session II – Mechanisms of Radiation-Induced Damage & Repair, Session III – Biodosimetry (Biomarker and Method Validation & Device Design), and Session IV – Training & Education/Pilot Projects Updates.

About the Meeting Attendees

Among the over 100 participants were CMCR Principal Investigators (PIs) and their staff, NIAID representatives, and contractors receiving funding for product development support for radiation countermeasures. There were also scientists from the United States national research laboratories (Lawrence Livermore, Pacific Northwest), DoD, and other government agencies (National Cancer Institute, Armed Forces Radiobiology Research Institute, Centers for Disease Control, Defense Advanced Research Projects Agency, Defense Threat Reduction Agency, Department of Energy, Food and Drug Administration, Office for Public Health Emergency Preparedness, and the Office of Science and Technology Policy). Please note: Because confidential, pre-publication data were presented at the meeting, only brief summaries of the presentations will be presented as part of this report.

Meeting Summary – Day One

The day began with an update on the status of the program with regards to involvement of NIAID program staff (Dr. Narayani Ramakrishnan). Attendees next heard about the productivity of the steering committee in the first 9 months of the program, including teleconference communications that had occurred between the CMCR PIs, as well as the meetings that had been planned and carried out with the FDA, and between the Centers (Dr. Paul Okunieff). Participants in the meeting next heard brief comments about the role of the CMCR program in the government effort to prepare for a radiological emergency (Dr. Richard Hatchett).

The first part of Session I included projects on the development of radiation countermeasures for early effects, including the hematopoietic and gastrointestinal symptoms of acute radiation syndrome (ARS). Topics covered included: 1) identifying potential mitochondrial targets for radioprotection, and Mn-SOD therapy (Pittsburgh Group); 2) use of growth hormones as a hematopoietic radioprotectant (Duke Group); 3) inhibitory hormone analogs as agents for radiation-induced gastrointestinal (GI) injury (Duke Group-University of Arkansas); and 4) developing enzyme inhibitors and receptor inhibitors to mitigate radiation damage to the GI tract (Wisconsin Group).

The next segment of Session I addressed mitigation/treatment of the late effects of radiation exposure, including damage to the lungs, kidneys and central nervous system. Presentations included: 1) ACE

inhibitors to treat chronic renal injuries (Wisconsin Group); 2) ACE inhibitors & SOD mimetics to treat radiation-induced CNS injury (Wisconsin Group – Henry Ford Hospital); 3) development of a lung injury model to look for changes in pulmonary vasculature after radiation exposure (Wisconsin Group); and 4) SOD/Catalase mimetics and ACE inhibitors to mitigate radiation-induced lung damage (Wisconsin Group – University of Toronto).

Attendees next heard about the advances in cell-based therapies being made at the Fred Hutchinson Cancer Research Center. These projects included research on the possible use of: 1) myeloid progenitor cells, 2) umbilical cord blood, and 3) HLA-mismatched or HLA-haploidentical donor in hematopoietic cell transplants.

In the final segment of Session I, two centers carrying out compound screening protocols discussed their progress in narrowing the search for novel radiation countermeasures. Screens being carried out by the UCLA group include compound identification using: 1) a bioluminescent, high-throughput yeast assay, 2) a T-lymphocyte assay, and 3) an assay utilizing cells from patients with known or undiagnosed DNA repair disorders. Screens being done by the Dana Farber group centered on identifying radioprotective agents using cell-based small molecule drug screens, as well as genome-wide RNAi screens.

Beginning late in the day, Session II dealt with the study of the mechanisms involved in radiation induced damage and repair. Presentation topics included the role of: 1) cyclins and cyclin-dependent kinases in radiation-induced apoptosis (Dana Farber Group); 2) Wnt signaling in repair of HSC damage (Duke Group); 3) endothelial cell factors in repair of the hematopoietic compartment (Duke Group), 4) TLR-signaling molecule, MyD88 in radiation-induced pneumonitis (Duke Group), 5) enteric microbes in radiation-induced GI-injury (Duke Group); 6) cardiolipin oxidation in radiation-induced apoptosis (Pittsburgh Group), and 7) mechanisms of radiation damage to the mitochondrial electron transport chain (Pittsburgh Group).

Meeting Summary – Day Two

Day two began with Session III, detailing advances by the Centers in defining potential biomarkers to assess radiation exposure, and the design and fabrication of devices that can rapidly and accurately determine an individual's radiation dose received. Research updates on devices included: 1) advances in creating a field-deployable device to assess radiation exposure by measuring EPR signatures in human teeth (Rochester Group), 2) development of a hand-held, metabolomics-based biodosimeter (Columbia Group), and 3) design of an automated, robotic unit for image analysis of cytogenetic radiation markers (Columbia Group).

In the next segment of Session III, dealing with Cytogenetics, Proteomics and Metabolomics studies being carried out by the Centers, research included: 1) micronuclei analysis in lymphocytes (Columbia Group) and micronuclei and radiation-induced foci analysis in skin (Rochester Group), 2) metabolomics signature of radiation (Columbia Group), 3) flow cytometry assays to detect micronucleated reticulocytes as markers of radiation damage (Rochester Group), and 4) identification of RNA transcripts (Duke and Fred Hutchinson Groups) and/or proteins in blood (Fred Hutchinson Group), the levels of which change following radiation exposure.

The open session of the CMCR meeting concluded with Session IV - reports on the progress on the Education and Training and Pilot Project Cores that are common to all the Centers. The CMCR meeting ended with a closed business meeting in the afternoon for the CMCR steering committee. This committee included the CMCR PIs, as well as relevant NIH and DHHS staff.